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(54) Title: NEW INDICATION FOR USE OF ANTIEPILEPTIC AGENTS AND MEDICINES

(57) Abstract

This invention refers to medicine, in particular to pharmacology and pharmacotherapy. The technical result is to prevent specific expiratory bronchospasm in patients with bronchial asthma and other diseases and pathological conditions. The principally new indication provides use of antiepileptic agents for treatment of all types of bronchial asthma, status asthmaticus, asthmatic and allergic bronchitis, bronchial hyperreactivity and bronchospastic syndromes and treatment of diseases proceeding with these syndromes and also for treatment of allergic and vasomotor rhinitis and rhinoconjunctivitis.

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NEW INDICATION FOR USE OF ANTIEPILEPTIC AGENTS AND MEDICINES

Technical Field

This invention refers to medicine, in particular to pharmacology and pharmacotherapy.

Background Art

Antiepileptic agents and medicines are used in the following directions: for treating epilepsy, seizures and similar conditions, trigeminal and other neuralgia, hemicrania, breath-holding attacks, tic hyperkynesia, psychosis, abstinent syndromes and some other diseases (Mashkovskij MD. Medicinal Agents. Moscow, "Meditsina", 1998).

The use of antihystamines for treatment of bronchial asthma, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndrome for treatment of diseases and pathological conditions with these syndromes (Mashkovskij MD. Medicinal Agents. Moscow, "Meditsina", 1998).

The use of steroid hormones for treatment of bronchial asthma, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes and for treatment of diseases and pathological conditions with these syndromes (Mashkovskij MD. Medicinal Agents. Moscow, "Meditsina", 1998)

The use of beta-2 agonists for treatment of bronchial asthma, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes and for treatment of diseases and pathological conditions with these syndromes (Mashkovskij MD. Medicinal Agents. Moscow, "Meditsina", 1998)

The use of theophilline for treatment of bronchial asthma, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes and for treatment of diseases and pathological conditions with these syndromes (Mashkovskij MD. Medicinal Agents. Moscow, "Meditsina", 1998)

The use of H1 and H2 leukotriene antagonists for treatment of bronchial asthma, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes and for treatment of diseases and pathological conditions with these syndromes (Riboux JP. The allergic reaction. USB Pharmaceutical Sector -Braine l'Alleud, 1993)

The following disadvantages were revealed under their application:

- excessive individual action and inadequate effectiveness;
- negative influence upon cardiovascular functions and hypertensive effect;
- negative influence upon hormonal balance and due to that the systemic side effect

- frequent and depending on circumstances irregular introduction of some medicines through respiratory tract into organism by technical means (inhalation, etc.).

Technical result is achieved by introducing antiepileptic agents into organism by the known way (perorally, parenterally, inhallationally, through mucous membranes of organism, transcutaneously, by using electrophoresis, phonophoresis and other methods; as ointments, per rectum, etc.) in ordinary or individually selected dose. During continuous, long-term administration of these agents in the patients the attacks of bronchial asthma and bronchospasms are not observed or such attacks are observed significantly less frequently than before administration of these agents.

Disclosure of the Invention

Use of antiepileptic agents and their derivates and analogues, their tautomers and pharmaceutically accepted compounds separately or in combination with other agents as therapeutic means for treating of all types of bronchial asthma, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes and treatment of diseases proceeding with these syndromes and also for treatment of allergic and vasomotor rhinitis and rhinoconjunctivitis.

Antiepileptic agents with antiasthmatic properties include such agents as derivates, analogues and tautomers of 1) barbituric acid, 2) hydantoin (e.g. phenytoin, fosphenytoin), 3) pyrimidine (e.g. hexamidinum, primidone), 4) oxazolidinedione (e.g. trimethindione), 5) indandione (e.g. methindion), 6) succinimide (e.g. aethosuximide), 7) iminostilben (e.g. carbamazepine, oxcarbazepine), 8) butamsultham (e.g. sultiam), 9) 1,4 benzodiazepines (e.g. clonazepam), 10) 1,5 benzodiazepines (e.g. clobazam), 11) valproic acid and salts of valproic acid, 12) aminoindandions (e.g. methindione), 13) acethylcarbamate (e.g phenacemide), 14) beta-chlorpropionic acid (e.g. beclamide), 15) tetronic acid (e.g. losigamone), 16) sulfonamides (e.g. zonisamide), 17) fructose sulfamates (e.g. topiramate), 18) pyrrolidine (e.g. levetiracetam), 19) acetamides (e.g. remacemide hydrochloride), 20) propylene glycols (e.g. felbamate), 21) nipecotic acid (e.g. tiagabine), 22) triasines (e.g. lamotrigine), 23) gamma-aminobutyric acid (e.g. vigabatrin, gabapentin, progabide), 24) thiazoles (e.g. ralitoline) 25) selenazoles, 26) pirazoles, 27) izatine, 28) diphenylsulphone, 29) ethylselenazolidindione, 30) benzimidazolin-2tione, 31) dioxolanes (e.g. stiripentol), 32) azetidines, 33) triazoles (e.g. loreclezole), 34) acetamides (e.g. milacemide), 35) imidazoles (e.g. nafimidone) and other antiepileptic agents.

In comparison to the known prior art when applying antiepileptic agents as medicines for treatment of bronchial asthma, asthmatic and allergic bronchitis, syndrome of bronchial hyperreactivity and bronchospastic syndrome and illnesses proceeding with these syndromes:

- significantly higher treatment efficiency is marked;
- negative influence upon cardiovascular system and hypertensive effect is not marked;
- negative influence upon hormonal exchange and in this view injuring system influence upon organism is not marked;
- there is no need in frequent and depending on the circumstances irregular introduction into organism of some medical preparations through respiratory tract by technical means.

Scientific Background:

According to the joint definition of WHO and US National Institute of Heart, Blood and Lung, bronchial asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and T-lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli (Global Initiative for Asthma. National Institutes of Health. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Publication no. 95-3659, 1995).

The cause of asthma is unknown, and it is not even clear whether asthma is a single disease with a single cause or a symptom complex with many separate causes (Reed CE. Allergy and asthma. In: Sodeman's pathologic physiology. Mechanisms of disease. Ed.: W.A.Sodeman, T.A.Sodeman. W.B. Saunders Company. Philadelphia, London, Toronto, Mexico City, Rio de Janeiro, Sydney, Tokyo, Hong Kong, 1985).

We presume, that bronchial asthma and epilepsy have some similarities in pathogenic mechanisms.

This could be confirmed by the following facts:

1) Both diseases are hyperreactivity disorders with paroxysmal clinical manifestations. Both diseases have hereditary predisposition and manifestation of the symptoms depends on the influence of additional external factors.

2) According to the indirect theory of pathogenesis of asthmatic bronchoconstriction (Leff A. Pathophysiology of asthmatic bronchoconstriction. Chest, no.1 (Suppl.): 135-215, 1982) the

central nervous system plays the important role for the development and realization of the bronchial ways hyperreactivity syndrome (Empey DW, Latinin LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Am. Rev. Respir. Dis., 113: 131-39, 1976;

Gold WM, Kessler GF, Yu DYC. Role of vagus nerves in experimental asthma in allergic dogs. J. Appl. Physiol., 33: 719-25, 1972; Leff A. Pathophysiology of asthmatic bronchoconstriction. Chest, no.1 (Suppl.): 135-215, 1982; Nadel JA. Neurophysiologic aspects of asthma. In: Asthma. Physiology, immunopharmacology, and treatment. Ed. by Austen F., Lichtenstein L. Academic Press, New York, San Francisco, London, 1973). There are experimental models of inducing expiratory bronchospasm by irritation of certain cerebral zones and it is shown the possibility of pharmacological correction of such bronchoconstriction with neurotropic agents (Khaunina RA. Action of neurotropic drugs on central bronchospasm (Eng. abstr.). [Russian]. In: Researches in pharmacology of reticular formation and synaptic transmission, p.205-210. Ed. by A.V. Valdman. Leningrad, 1961; Pekker IL. Zhaugasheva SK. New experimental data about influence of mesoxiflurane on bronchial permeability in cats [Russian]. In: Pathology of respiratory organs, pp.55-56. Leningrad, 1973; Pekker IL, Zhaugasheva SK, Balkhanova SA. Influence of some medicines on bronchial permeability in experimental investigations and in clinical practice [Russian]. In: Pathology of respiratory organs, pp. 41 - 44. Leningrad, 1975; Zhaugasheva SK. Pharmacology of experimentally induced bronchospasm [Russian]. Zdravookhranenie Kazakhstana, (3): 64-66, 1975; Zhaugasheva SK. The effect of halidor on experimental bronchial spasm (Eng.abstr.).[Russian]. Farmakologiia i toksikologiia, 39(1): 50-53, 1976.

3) Concomitant development of bronchial asthma and schizophrenia in the same patient is very unusual (Dobrzanski T. Problems of internal pathology in patients with psychic disorders [Polish]. Panstwowy Zaklad Wydawniciw Lekarskich, Warszawa, 1970; Ehrentheil OF. Common medical disorders rarely found in psychotic patients. Arch. Neurol. Psychiat., 77(2): 178-86, 1957), and this fact is in accordance with the well-known phenomenon of clinical antagonism of the epileptic seizures and schizophrenic psychosis (Meduna K. Die Konvulsionstherapie der Schizophrenia. Halle, 1937). In case of combination of bronchial asthma and schizophrenia, the worthening of schizophrenia is accompanied with the amelioration of bronchial asthma symptoms and vice versa (Funkenstein, DH. Psychophysiologic relationship of asthma and urticaria to mental illness. Psychosom. Med., 12: 377-85, 1950; Lemke MR. Anti-cyclic manifestation of asthma bronchiale and schizophrenic psychosis [German]. Fortschritte der Neurologie-Psychiatrie, 60(12): 477-80, 1992).

4) Epilepsy and seizure syndromes are present in anamnesis of children with bronchial asthma 2 - 6.5 times more often than among total children population (Ivanova NA.Epilepsy in structure of concomitant diseases in children with bronchial asthma and principles of complex therapy [Russian]. In: Modern principles of treatment of children with relapsing and chronic bronchial and lungs diseases, pp. 89-91. Leningrad, 1987; Ivanova NA. Psychoneurological disorders in children with bronchial asthma [Russian]. Voprosy oxrany materinstva i detstva, (5): 57-60, 1989). There are some correlations in the changes of concentration of neuroactive metabolites of tryptophan in biological fluids in children with epilepsy and bronchial asthma (Ivanova NA, Ryzhov IV., Budzin VV, Nikitina ZS. Elevated kinurenine concentration in the blood serum of children with epilepsy and bronchial asthma. [Russian]. Zhurn. Nevropatol. i Psikhiatr., 88 (6): 21-24, 1988).

5) One of the main clinical symptoms of bronchial asthma is paroxysmally induced bronchoconstriction and breathlessness (dyspnoe) with difficulties in expiration, while inspiration is almost intact. The asthmatic person usually can inspire quite adequately but has great difficulty expiring (Guyton AC. Textbook of medical physiology. W.B. Saunders Company, Harcourt Brace Jovanovich, Inc. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo, 1991). This is a differential factor of bronchial asthma from many other respiratory tract pathologies (Vinogradov AV. Differential diagnostics of internal diseases [Russian]. Meditsina, Moscow, 1987). At the same time we would like to underline the presence of another pathology of the respiratory tract with paroxysmally induced difficulties in expiration. There are cyanotic breath-holding attacks in children with the main symptom of paroxysmal breath stopping in the phase of inspiration and hindered or transitory impossibility of expiration. During pallid breath-holding attacks paroxysmal breath stop usually is additionally associated with reversible decrease of heart rate or asystole (Chutorian AM. Paroxysmal disorders of childhood. In: Rudolph's Pediatrics, 19th edition. Ed. by A.M. Rudolph, J.I.M. Hoffman, C.D. Rudolph, P. Sagan. Appleton & Lange, Norwalk, Connecticut/San Mateo, California, 1991). Increased vagal tone and vagal reflex overactivity usually are the causes of these paroxysms (Huttenlocher PR. The nervous system. In: Nelson textbook of pediatrics. Ed.: R. Behrman, V.C. Vaughan. W.B. Saunders Company, Harcourt Brace Jovanovich, Inc. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo, 1987; Korovin AM. Seizure conditions in children. Meditsina, Leningrad, 1984). Atropine and antiepileptic drugs are the first choice drugs in such patients (Chutorian AM. Paroxysmal disorders of childhood. In: Rudolph's Pediatrics, 19th edition. Ed. by A.M. Rudolph, J.I.M. Hoffman, C.D. Rudolph, P. Sagan. Appleton & Lange, Norwalk, Connecticut/San Mateo, California, 1991; Shanko, GG.

Respiratory affective paroxysms [Russian]. In: Encyclopedia of pediatrist neurologist, pp.405 - 406. Belaruskaya Entsiklapedyja, Minsk, 1993). It is considered that breath-holding attacks have pathogenic relationship with epilepsy and seizure syndromes (Kharitonov RA, Ryabinin MV, Kel'in LL. Affective respiratory attacks (clinical aspects, pathogenesis and rehabilitation) [Russian]. Zhurn. Nevropatol. i Psikhiatr., 90(6): 5-10, 1990). 3.6% of persons with breath-holding attacks in childhood lately became epileptic patients (Shanko, GG. Respiratory affective paroxysms [Russian]. In: Encyclopedia of pediatrist neurologist, pp.405 - 406. Belaruskaya Entsiklapedyja, Minsk, 1993) and this is 3.6-7.2 time more frequent prevalence of epilepsy in compare to total population - approximately 0.5-1% (Ehle A, Homan R. The epilepsies. In: Neurology. Ed.: R.N. Rosenberg. Grune & Stratton. New York, London, Toronto, Sydney, San Francisco, 1980;

Shanko GG. Epilepsy [Russian].. In: Encyclopedia of pediatrician neurologist, pp. 538-546. Belaruskaya Encyklapedya, Minsk, 1993; Zielinski JJ. Epidemiology. In: A Textbook of Epilepsy. Ed.: J. Laidlaw, A. Richens, J. Oxley. Churchill Livingstone, Edinburgh, London, Melbourne, New York, 1988). Several authors report, that in children with breath-holding attacks the epilepsy develops in 12% of cases (Ratner A.Y. Natal injuries of nervous system. [Russian]. Kazan University Publishing House, 1985). According to another data, among 700 patients with epilepsy the breath-holding attacks were observed in anamnesis in 49 patients (7%) (Kharitonov RA, Ryabinin MV, Kel'in LL. Affective respiratory attacks (clinical aspects, pathogenesis and rehabilitation) [Russian]. Zhurn. Nevropatol. i Psikhiatr., 90(6): 5-10, 1990). According to our observations 13.5% of children with bronchial asthma have breath-holding attacks in anamnesis, which is 2.7-3.4 times higher in comparison with other total children population - 4-5% (Shanko, GG. Respiratory affective paroxysms [Russian]. In: Encyclopedia of pediatrist neurologist, pp.405 - 406. Belaruskaya Entsiklapedyja, Minsk, 1993). Consequently, we can hypothesize, that bronchial asthma, epilepsy and breath-holding attacks have certain pathogenic interrelationships.

6) In bronchial asthma (Global Initiative for Asthma. National Institutes of Health. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Publication no. 95-3659, 1995) as well as in epilepsy (Karlov VA. Epilepsy [Russian]. Meditsina, Moscow, 1990) hyperventilation frequently provokes asthmatic attacks and seizures accordingly. Some other factors, such as emotions, intensive smell, meteorological and endocrine factors also could provoke paroxysms of epilepsy (Biniaurishvili RG, Vein AM. Gafurov BG. Rakhimdzhanov AR. Epilepsy and functional status of brain [Russian]. Meditsina UzSSR, Tashkent, 1985) as well as that of bronchial asthma (Global Initiative for Asthma. National Institutes of Health. Global

strategy for asthma management and prevention. NHLBI/WHO workshop report. Publication no. 95-3659, 1995).

7) We investigated EEG-computer topography in 75 patients with bronchial asthma (Lomia M., Pruidze M., Kharatishvili I. Neurological and EEG-computer topographic studies in adults with bronchial asthma. Georgian Medical News, 1997, no.10 (31), pp.29-31; Pruidze M., Lomia M., Manjgaladze N. Disturbances of brain bioelectric activity in patients with bronchial asthma and their correlation with other asthmatic clinical symptoms. In: Actual problems of medicine. Materials of Conference, dedicated to memory of Simeon Kipshidze. Tbilisi 1997, pp. 35-38), In 65 (86.7%) from 75 patients with bronchial asthma the different EEG disturbances were registered, but we did not registered typical epileptic patterns of EEG activity in our patients. We also did not registered in asthmatic patients any correlation of decreased seizure threshold on EEG with bronchial hyperreactivity. This fact can be explained by abnormally increased vagal tone, which restricts expansion of convulsive activity into other parts of CNS: as it is known vagal stimulation was successfully introduced recently for management of epilepsy if unresponsive to pharmacotherapy (Schachter SC. Saper CB. Vagus nerve stimulation. [Review]. Epilepsia, 39(7):677-86, 1998). In spite of this, we suppose that bronchial hyperreactivity syndrome in bronchial asthma could be considered as the analogue of the increased seizure susceptibility (predisposition) in epilepsy.

8) Epilepsy most often develops at the age under 16-24 years (Brain WR, Walton JH. Brain's diseases of nervous system. Oxford University Press. Oxford, New York, Toronto, 1977; Fry J. Common diseases: their nature, incidence and care. Medical and Technical Publishing Co., Ltd. Lancaster, 1974; Goldensohn ES, Glaser GH, Goldberg MA. Epilepsy. In: Merritt's textbook of neurology. Ed.: L.P. Rowland. Lea & Febiger. Philadelphia, 1989; Karlov VA. Epilepsy [Russian]. Meditsina, Moscow, 1990; Saradjishvili PM, Bibileishvili SI, Gabashvili VM, Alekseeva GV, Zemskaya AG, Morgunov VA, Tiganov AS, Shumskij NG, Skvortsov IA. Epilepsy [Russian]. In: Great Medical Encyclopedia, vol. 28, pp. 291-305. Sovetskaya Entsiklopediya, Moscow, 1986), the next slight peak in morbidity is after the age of 40 -50 (Brain WR, Walton JH. Brain's diseases of nervous system. Oxford University Press. Oxford, New York, Toronto, 1977; Fry J. Common diseases: their nature, incidence and care. Medical and Technical Publishing Co., Ltd. Lancaster, 1974; Karlov VA. Epilepsy [Russian]. Meditsina, Moscow, 1990). This is very similar to the incidence of bronchial asthma: in more than half of the cases bronchial asthma begins in childhood (Chuchalin AG. Bronchial asthma [Russian]. Meditsina, Moscow, 1985; Fry J. Common diseases: their nature, incidence and care. Medical and

Technical Publishing Co., Ltd. Lancaster, 1974), the second slight peak in number of incidences comes after the age of 35 - 45 years (Fedoseev GB, Khlopotova GP. Bronchial asthma [Russian]. Meditsina, Leningrad, 1988; Fry J. Common diseases: their nature, incidence and care. Medical and Technical Publishing Co., Ltd. Lancaster, 1974). Seizure susceptibility or convulsive predisposition (Badalyan LO, Golubeva EL. Seizures [Russian]. In: Great Medical Encyclopedia, vol. 24, pp. 348-352. Sovetskaya Entsiklopediya, Moscow, 1985; Biniaurishvili RG, Vein AM. Gafurov BG. Rakhimdzhanov AR. Epilepsy and functional status of brain [Russian]. Meditsina UzSSR, Tashkent, 1985) as well as bronchial reactivity (O'Connor GT, Weiss ST, Speizer FE. The epidemiology of asthma. In: Bronchial asthma. Ed. by Gershwin M.E. Grune aud Stratton, New York, 1986) is considerably decreased after the age of 16.

9) According to our data the state similar to aura can be observed before the asthmatic attacks. We have interviewed patients with bronchial asthma using special questionnaire designed for this purpose; 31.5% of patients reported the presence of symptoms, preceding the attacks by several minutes or seconds - more often sensation of compression or tickling in the throat and/or nasal cavity, or restrain and compression in chest. Besides, in several patients with bronchial asthma we observed prodromal syndromes preceding exacerbation of the disease by several days (mood disorders, irritability, anxiety, etc.), which can be analogues of the prodromal premonitory epileptic syndromes.

Based on these considerations, bronchial asthma can be considered as pathologic condition with paroxysmal clinical manifestation; paroxysms of bronchial asthma by the relative analogy with "Clinical and electroencephalographical classification of epileptic seizures" (Commission on Classification and Terminology of the International League against Epilepsy, 1981. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia, 22: 489-501, 1981), can be conditionally considered as a condition similar to the simple partial seizure with autonomic visceral manifestations in the form of spasm of bronchial smooth muscles mostly in the phase of expiration, induced predominantly as reflex (respiratory tract allergy or/and infection, nasal polyposis, inhalation of cold and/or dry air, intensive smell, etc.) or psychogenic (emotiogenic) reaction. It can be considered, that reflexes from bronchial surface and in some cases from other sites, or psychogenic factors can cause centrally induced neurogenic (vagal, and not only vagal) paroxysmal bronchoconstriction with predominantly expiratory dyspnoe and neurogenic bronchial inflammation due to decreased excitation threshold of the corresponding areas of central nervous system. This spasm (reflex or psychogenic) can be a result of the allergen effects with subsequent inflammation, or also intensive smell, cold air,

emotional factors, physical exercise, signals from the interoceptors of other organs, etc. As a rule, the bronchial spasm is partial - it almost never is generalized and never accompanied with the disturbances of consciousness. Similar to the epileptic status an asthmatic status could be developed.

Based on the above-mentioned considerations, we assume that:

Bronchial asthma is a disease with the complex pathogenic mechanism, including two components: 1) peripheral (allergic, reflex, physical exercise) and/or central (psychogenic) **trigger** component and 2) central neurogenic **generator** component of paroxyzmal attacks of bronchoconstriction and inflammation. Under the influence of trigger components (in case of constitutional predisposition to the development of generator component - decrease of threshold to the central neurogenic predisposition (susceptibility) to the paroxysmal bronchoconstriction and concomitant neurogenic inflammation) the paroxysmal generator component is induced and pathologic process maintained, manifesting itself with the periodic paroxysmal bronchial smooth muscles spasms, predominantly in the phase of expiration induced by the central nervous system. These spasms are clinically manifested by the paroxysmal attacks of specific predominantly expiratory dyspnoe and/or cough.

The effect of generator component results in the maintenance and stabilization of trigger components, manifested in the additional neurogenic induction and sustaining of chronic allergic bronchial inflammation, acquiring additional neurogenic features, and to the increase of reactivity in paroxysm-generating neuronal structures, which results in the appearance of the new, secondary trigger factors capable of inducing paroxysm (so called "asthmatization" of the pathologic state (Fuchs E. Bronchial asthma. Sandoz, Berne, 1981)) which is similar to the formation of the new, secondary trigger foci of epileptic activity in epilepsy.

Thus, circulus vicious is formed: trigger factors provoke activity of generator factor, and vice versa. We suppose, that this is a mechanism of chronization of asthma.

Syndrome of bronchial hyperreactivity, occult (Leff A. Pathophysiology of asthmatic bronchoconstriction. Chest, no.1 (Suppl.): 135-215, 1982; Williamson HA Jr. Schultz P. An association between acute bronchitis and asthma. Journal of Family Practice, 24(1):35-8, 1987) or latent bronchospasm, airway resistance, edema and chronic inflammation of respiratory tract can be considered as increased asthmatic susceptibility (predisposition), induced by the central neurogenic generator component. This increased asthmatic susceptibility (predisposition) is analogue of the increased seizure susceptibility (predisposition) in epilepsy, and asthmatic status can be considered as a certain analogue of the epileptic status. Attenuation of the trigger, as well

as the generator central neurogenic paroxysmal component results in the disappearance of the clinical manifestations of the disease. Very often it is not possible to determine exactly the nature of the trigger factors (especially with their variety), which makes it difficult to influence them by pharmaceutical agents or other methods. Consequently, therapeutic interventions aimed at the paroxysm - generating factors are more justified - e.g. anticonvulsive agents. This class of medication has been successfully applied by us.

The possible trigger factors and mechanisms are as follows: allergy and allergic inflammation in respiratory tract, infections of respiratory tract, pathological changes in upper respiratory tract (predominantly in nasopharynx: adenoids, chronic inflammation, etc.) and nasal cavity, physical exercise, hyperventilation, inspiration of dry or cold air, psychogenic factors, intensive smell, inspiration of irritating substances, meteorological factors, allergic processes outside respiratory tract, irritation of interoceptors, endocrine disorders, non-steroidal anti-inflammatory drugs, etc.

Trigger factors are well studied, but exact location of central neurogenic generating structures of bronchial asthma is still unknown, and we do not know, in which limited neuronal populations the increased activity and/or paroxysmal discharges occurs, and which structures of CNS have relationship to this process. It is without doubt that vagus nerve, central and peripheral structures of parasympathetic autonomic nervous system, some structures of brain stem, limbic system, certain areas of hypothalamus and the central nervous system structures related to them are involved in this process.

The fact, that generalization of paroxysmal activity never occurs in bronchial asthma, can be explained by abnormally increased vagal tone, which restricts expansion of convulsive activity into other parts of CNS: as it is known vagal stimulation was successfully introduced recently for management of epilepsy if unresponsive to pharmacotherapy (Schachter SC. Saper CB. Vagus nerve stimulation. [Review]. Epilepsia, 39(7):677-86, 1998). In our opinion, all above mentioned explain the high efficacy of certain anticonvulsive agents in prevention of clinical manifestations of disease - paroxysms of expiratory breathlessness and cough. Long-term treatment decreases degree of latent bronchospasm and chronic inflammation of respiratory tract up to their complete disappearance. Withdrawal of anticonvulsive drugs can lead to the restoration of the initial status. Complete recovery is possible only with long-term treatment with antiepileptic agents. Probably, the duration of therapy is individual, like it is in epilepsy.

It is possible that efficacy of anticonvulsants in bronchial asthma is due not only to their central effect, but also to the local effect on the airways: reduction of sensitivity of local nerve

terminals, local anti-inflammatory effect, especially inhibition of axon reflexes, which are considered by some authors to be one of the mechanisms of neurogenic inflammation (Rihoux J-P. The allergic reaction. UCB Pharmaceutical Sector - Braine-l'Alleud, Brussels, 1993), inhibition of neuropeptide release from axon terminals in bronchial wall, reduction of peripheral neuromuscular transmission on periphery, local effect on cells membranes and direct relaxing effect on the bronchial smooth muscles and inhibition of post-tetanic depolarization. It is possible that anticonvulsive agents act similarly to the substances, reducing elevated vagal tonus and tonus of other nerves, and in this way cause bronchodilation and reduction of neurogenic inflammation. It is known, that vagal stimulation in experimental animals results in accentuation of neurogenic inflammation in airways (Morikawa M. Sekizawa K. Sasaki H. Inhibitory actions of cyclic AMP on neurogenic plasma extravasation in rat airways. European Journal of Pharmacology, 241(1):83-7, 1993.

It should also be considered, that anticonvulsants inhibit neuronal discharges of any kind: epileptogenic or non-epileptogenic. This property of anticonvulsants explains their efficacy in variety of non-epileptic conditions (Kryzhanovskii GN. Determinant structures in pathologic conditions of the nervous system. Generator mechanisms of neuropathologic syndromes. [Russian]. AMS USSR, Meditsina, Moscow, 1980). It is also possible, that anticonvulsants act via neurogenic control of immune reactions. Neurogenic control of immune reactions was first described at the beginning of the 20th century (Besredka A., Steinhardt E. Du mechanisme de l'antianaphylaxie. [French]. Ann.Inst. Pasteur, 21: 384, 1907), and confirmed later (Besedovsky HO, Sorkin E. Immunologic - neuroendocrine circuits: physiological approaches. In: Psychoneuroimmunology. Ed.: R. Ader. Academic Press. New York, London, Toronto, Sydney, San Francisco, 1981; Filipp G, Szentivanyi A, Mess B. Anaphylaxis and the nervous system. Acta Med. Acad. Sci. Hung., no.3, 163, 1952; Hall RN, Goldstein AL. Neurotransmitters and the immune system. In: Psychoneuroimmunology. Ed.: R. Ader. Academic Press. New York, London, Toronto, Sydney, San Francisco, 1981; Maclean D, Reichlin S. Neuroendocrinology and the immune process. In: Psychoneuroimmunology. Ed.: R. Ader. Academic Press. New York, London, Toronto, Sydney, San Francisco, 1981; Spector NH, Korneva EA. Neurophysiology, immunophysiology, and neuroimmunomodulation. In: Psychoneuroimmunology. Ed.: R. Ader. Academic Press. New York, London, Toronto, Sydney, San Francisco, 1981; Spiegel EA., Kubo K. Anaphylaxis and nervous system [German]. Zkrft. Exp. Med., 38: 458, 1923).

Until today, management of bronchial asthma was held in two main directions:

1) modification of factors inducing allergic reaction and interference on the certain stages of allergic reaction; and 2) interference with peripheral bronchial receptors. Both these directions do finally affect the trigger factors.

We suggest 3rd direction in the management of bronchial asthma: application of anticonvulsive agents for the control of activity of neurogenic generator mechanisms of bronchial asthma paroxysms or/and for the possible control of other mechanisms of bronchial asthma. This new approach leads to the prevention of paroxysms of bronchial asthma and opens up new perspectives for the management of this disease.

Bronchial asthma is not the only disease having pathogenic mechanisms similar to that of epilepsy. Trigeminal neuralgia being the condition of hyperreactivity with paroxysmal clinical manifestations has certain pathogenic similarity with epilepsy (Karlov VA. Poliantsev VA. Petrenko SE. Vilkov VG. Visual evoked potentials in patients with trigeminal neuralgia. [Russian] Zhurn. Nevropatol. i Psikhiatr., 83(5):692-6, 1983; Kryzhanovskii GN. Reshetniak VK. Igon'kina SI. Zinkevich VA. [Epileptiform activity in the somatosensory cortex of rats with trigeminal neuralgia]. [Russian] Biull. Eksper. Biol. Med., 114(8):126-8, 1992; Pagni CA. The origin of tic douloureux: a unified view. Journal of Neurosurgical Sciences, 37(4):185-94, 1993). It is considered that paroxysmal pain attacks in trigeminal neuralgia are associated with pacemaker activity similar to that in epilepsy in brain stem trigeminal nucleus (Pagni CA. The origin of tic douloureux: a unified view. Journal of Neurosurgical Sciences, 37(4):185-94, 1993), which is induced by slight tactile stimulation of trigger zone, sensory (tactile, auditory, photo or thermal stimulus), and psychoemotional factors, etc..Patients often report the presence of peculiar paraesthetic aura before the paroxysm (Grechko VE, Vasin NY, Minakova EI, Mikhajlov SS. Trigeminal nerve [Russian]. In: Great Medical Encyclopedia, vol. 25, pp. 289-297. Sovetskaya Entsiklopediya, Moscow, 1985). It is suggested, that not only trigeminal nuclei but also other upper regions of CNS may play a role in the generation of pain paroxysms (Kryzhanovskii GN. Determinant structures in pathologic conditions of the nervous system. Generator mechanisms of neuropathologic syndromes. [Russian]. AMS USSR, Meditsina, Moscow, 1980). Some authors suggest, that trigeminal neuralgia has a peripheral cause and a central pathogenesis (Fromm GH, Terrence CF, Maroon JC. Trigeminal neuralgia. Current concepts regarding etiology and pathogenesis. Arch. Neurol, 41:1204-1207, 1984). Chronic "irritation" of the peripheral trigeminal nerve leads to failure of segmental inhibition in the trigeminal nucleus and to production of ectopic action potentials in the trigeminal nerve. Increased neuronal discharge and reduced inhibitory mechanism produce a hyperactive sensory

circuit, leading eventually to paroxysmal discharges in the trigeminal nucleus (Dalessio DJ. The major neuralgias, postinfection neuritis, and atypical facial pain. In: Wolff's Headache and Other Head Pain, pp. 266-288. Ed.: D.J. Dalessio. Oxford University Press. New York, Oxford, 1987). The main reason for the efficacy of anticonvulsants in both epilepsy and trigeminal neuralgia may be the common pathogenic mechanism of these conditions (Karlov VA, Savitskaya ON. Neuralgia of the trigeminal nerve (Eng. abstr.).[Russian]. Zhurn. Nevropatol. i Psikhiatr., 76(6): 822-826, 1976; Kryzhanovskii GN. Determinant structures in pathologic conditions of the nervous system. Generator mechanisms of neuropathologic syndromes. [Russian]. AMS USSR, Meditsina, Moscow, 1980). As in the case with bronchial asthma, one of the pathogenic mechanisms of trigeminal neuralgia is the neurogenic inflammation in which neuropeptides play a role (Strittmatter M, Grauer M, Isenberg E, Hamann G, Fischer C, Hoffmann KH, Blaes F, Schimrigk K. Cerebrospinal fluid neuropeptides and monoaminergic transmitters in patients with trigeminal neuralgia. Headache, 37(4):211-6, 1997).

Migraine also has similarity with epilepsy. Migraine is a disease of hyperreactivity with paroxysmal clinical manifestation. Several investigators consider that migraine and epilepsy have certain common pathogenic mechanisms (Donnet A. Bartolomei F. Migraine with visual aura and photosensitive epileptic seizures. Epilepsia, 38(9):1032-4, 1997; Terwindt GM, Ophoff RA, Haan J, Sandkuijl LA, Frants RR, Ferrari MD. Migraine, ataxia and epilepsy: a challenging spectrum of genetically determined calcium channelopathies. Dutch Migraine Genetics Research Group. [Review]. European Journal of Human Genetics, 6(4):297-307, 1998). The aura is often observed before the migraine attacks, and migraine status may develop. Central structures of the nervous system are involved in pathogenesis of migraine paroxysms (Shtok VN. Headache [Russian]. Meditsina, Moscow, 1987). Migraine paroxysms can be triggered by auditory and photo stimulus, smells, psychoemotional factors, etc. As in bronchial asthma and trigeminal neuralgia the neurogenic inflammation is an important pathogenic mechanism of migraine (Hardebo JE. A cortical excitatory wave may cause both the aura and the headache of migraine. [Review] Cephalalgia, 12(2):75-80, 1992). Besides, it is known that migraine is more common in patients with bronchial asthma, than it is in the entire population, and vice versa (Chen TC, Leviton A. Asthma and eczema in children born to women with migraine. Archives of Neurology, 47(11):1227-30, 1990). Epilepsy is more common in patients with migraine, then in the general population, and vice versa (Alberca R. Epilepsy and migraine. [Review] [Spanish] Revista de Neurologia. 26(150):251-5, 1998).

In our opinion, bronchial asthma, trigeminal neuralgia and migraine can be included in the distinct group of paroxysmal neurogenic diseases, having pathogenic mechanisms similar to epilepsy. There may be approaches at different levels for the management of these diseases:

1) peripheral trigger or humoral level with specific effective groups of medications (e.g. non-steroidal anti-inflammatory drugs are effective for the treatment of migraine and trigeminal neuralgia, but at the same time they are contraindicated in bronchial asthma; β_2–adrenomimetics are effective for bronchial asthma, but β_2–adrenoblockers - for migraine, and at the same time β_2–adrenoblockers are contraindicated in bronchial asthma).

2) on the level of central neurogenic paroxysmal and inflammatory factors: in bronchial asthma (our data), migraine (Shelton CE., Connelly JF. Valproic acid: a migraine prophylaxis alternative. [Review]. Annals of Pharmacotherapy, 30(7-8):865-6, 1996; Wauquier A. Is there a common pharmacological link between migraine and epilepsy?. [Review]. Functional Neurology, 1(4):515-20, 1986; Ziegler DK. The treatment of migraine. In: Wolff's Headache and Other Head Pain, pp. 87-111. Ed.: D.J. Dalessio. Oxford University Press. New York, Oxford, 1987) and trigeminal neuralgia (Dalessio DJ. The major neuralgias, postinfection neuritis, and atypical facial pain. In: Wolff's Headache and Other Head Pain, pp. 266-288. Ed.: D.J. Dalessio. Oxford University Press. New York, Oxford, 1987; Karlov VA, Savitskaya ON. Neuralgia of the trigeminal nerve (Eng. abstr.).[Russian]. Zhurn. Nevropatol. i Psikhiatr., 76(6): 822-826, 1976) basic administration of anticonvulsive agents significantly decrease frequency and intensity of disease attacks.

In conclusion, our results demonstrate high efficacy of anticonvulsive drugs (carbamazepine and other anticonvulsants, including drugs of new generation) in management of bronchial asthma. This data opens up novel approach in the treatment of bronchial asthma as well as new areas of application for antiepileptic agents.

Examples:

Treatment of patients with bronchial asthma.

1) Patient P.L. 56 years, female.

Diagnosis - bronchial asthma, mixed form, severe degree. Accompanying disease - allergic rhinitis. She has been sick since 1986, was treated in many cities of the former USSR, but in spite of that the frequent attacks of asthma (up to several a day) were observed with the patient. Use of anticonvulsive medicine carbamazepine was started on October 26, 1996. In 5 days the asthmatic attacks stopped, after that the patient during more than five years she takes only antiepileptic agents (carbamazepine, oxcarbazepine, salts of valproic acid, phenytoin, fosphenytoin,

lamotrigine). During this time the attacks of asthma were not observed with the patient. At present, Peak Expiratory Flow Volume Rate of the patient is within the normal limits. Before the treatment with anticonvulsants the patient did not experience such long period without asthmatic attacks.

2) Patient M.S. 16 years, female.

Diagnosis - bronchial asthma, mixed form, severe degree. He has been sick since 1982, was treated in many clinics, but in spite of that the frequent attacks of asthma (up to 5-7 a week) were observed with the patient. Use of anticonvulsive medicine valproic acid was started on December 15, 1996. In 6 days the asthmatic attacks stopped, after that the patient during more than five years she takes only antiepileptic agents (valproic acid, lamotrigine, felbamate). During this time the attacks of asthma were not observed with the patient. At present, Peak Expiratory Flow Volume Rate of the patient is within the normal limits. Before the treatment with anticonvulsants the patient did not experience such long period without asthmatic attacks.

3) Patient S.G. 16 years, male.

Diagnosis - bronchial asthma, mixed form, severe degree. He has been sick since 1982, was treated in many clinics, but in spite of that the frequent attacks of asthma (up to 5-7 per month) were observed with the patient. Use of anticonvulsive medicine tiagabine was started on January 25, 1997. In 8 days the asthmatic attacks stopped, after that the patient during more than three years he takes only antiepileptic agents (zonizamide, methindion, topiramate). During this time the attacks of asthma were not observed with the patient. At present, Peak Expiratory Flow Volume Rate of the patient is within the normal limits. Before the treatment with anticonvulsants the patient did not experience such long period without asthmatic attacks

4) Patient C.N. 46 years, female.

Diagnosis - bronchial asthma, mixed form, severe degree. She has been sick since 1978, was treated in many clinics, but in spite of that the frequent attacks of asthma (up to 2-3 per day) were observed with the patient. Use of anticonvulsive medicine aethosuximid was started on September 25, 1996. In 4 days the asthmatic attacks stopped, after that the patient during more than 4 years she takes only antiepileptic agents (aethosuximid, clonazepam, hexamidin). During this time the attacks of asthma were not observed with the patient. At present, Peak Expiratory Flow Volume Rate of the patient is within the normal limits. Before the treatment with anticonvulsants the patient did not experience such long period without asthmatic attacks

5) Patient B.D. 53 years, male.

Diagnosis - bronchial asthma, mixed form, moderate degree. He has been sick since 1988, was treated in many clinics, but in spite of that the frequent attacks of asthma (up to 2-6 per month) were observed with the patient. Use of anticonvulsive medicine gabapentin was started on January 25, 1997. In next month the asthmatic attacks stopped, after that the patient during more than three years he takes only antiepileptic agents (gabapentin, vigabatrin, clobazam). During this time the attacks of asthma were not observed with the patient. At present, Peak Expiratory Flow Volume Rate of the patient is within the normal limits. Before the treatment with anticonvulsants the patient did not experience such long period without asthmatic attacks

6) Patient B.D. 53 years, male.

Diagnosis - bronchial asthma, mixed form, mild degree. He has been sick since 1985, was treated in many clinics, but in spite of that the frequent attacks of asthma (up to 8-9 per 1 months) were observed with the patient. Use of anticonvulsive medicine gabapentin was started on June 26, 1995. In next month the asthmatic attacks stopped, after that the patient during more than three years he takes only antiepileptic agents (gabapentin, progabide, clobazam). During this time the attacks of asthma were not observed with the patient. At present, Peak Expiratory Flow Volume Rate of the patient is within the normal limits. Before the treatment with anticonvulsants the patient did not experience such long period without asthmatic attacks

7) Patient N.L. 43 years, male.

Diagnosis - bronchial asthma, mixed form, moderate degree. He has been sick since 1980, was treated in many clinics, but in spite of that the frequent attacks of asthma (up to 1 per 1-2 days) were observed with the patient. Use of anticonvulsive medicine phenytoin was started on February 12, 1998. In next month the asthmatic attacks stopped, after that the patient during more than three years he takes only antiepileptic agents (phenytoin, remacemide hydrochloride, losigamone, levetiracetam). During this time the attacks of asthma were not observed with the patient. At present, Peak Expiratory Flow Volume Rate of the patient is within the normal limits. Before the treatment with anticonvulsants the patient did not experience such long period without asthmatic attacks.

CLAIMS

1) Use of antiepileptic agents, their derivates and analogues, their tautomers and pharmaceutically acceptable compounds comprising:

a) blocking induction of epileptic activity on endoneuronal level inhibiting "sudden" pacemaker activity and action of any epileptogenic factors and agents, and/or

b) affecting both an occurrence and dissemination of epileptogenic activity by suppressing pacemaker potentials, action potential of synaptic membrane, synaptic transmission by inhibiting sodium-dependent and/or other exciting postsynaptic potentials, and/or

c) impeding dissemination, generalization of epileptic activity and affecting mainly the synaptic formations, increasing brain inhibitory systems or decreasing brain excitation systems,

d) correcting, modulating and/or inhibiting paroxysmal descending impulses to respiratory ways from the central nervous system and paroxysmal activity induced in bronchial smooth muscles and/or induced therein, and/or

e) acting otherwise as medical means for treatment of all types of bronchial asthma, asthmatic status, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes, and for treatment of diseases and pathological conditions proceeding with these syndromes and also allergic and vasomotor rhinitis and rhinoconjunctivitis.

2) Usage of various antiepileptic agents from various chemical groups, according to item 1: derivates, analogues, tautomers and pharmaceutically acceptable compounds of 1) barbituric acid, 2) hydantoin (e.g. phenytoin, fosphenytoin), 3) pyrimidine (e.g. hexamidin, primidone), 4) oxazolidinedione (e.g. trimethindione), 5) indandione (e.g. methindion), 6) succinimide (e.g aethosuximide), 7) iminostilben (e.g. carbamazepine, oxcarbazepine), 8) butamsultham (e.g. sultiam), 9) 1,4 benzodiazepines (e.g. clonazepam), 10) 1,5 benzodiazepines (e.g. clobazam), 11) valproic acid and salts of valproic acid, 12) aminoindandions (e.g. methindione), 13) acethylcarbamate (e.g. phenacemide), 14) beta-chlorpropionic acid (e.g. beclamide), 15) tetronic acid (e.g. losigamone), 16) sulfonamides (e.g. zonisamide), 17) fructose sulfamates (e.g. topiramate), 18) pyrrolidine (e.g. levetiracetam), 19) acetamides (e.g. remacemide hydrochloride), 20) propylene glycols (e.g. felbamate) , 21) nipecotic acid (e.g. tiagabine), 22) triasines (e.g. lamotrigine), 23) gamma-aminobutyric acid (e.g. vigabatrin, gabapentin, progabide), 24) thiazoles (e.g. ralitoline) 25) selenazoles, 26) pirazoles, 27) izatine, 28) diphenylsulphone, 29) ethylselenazolidindione, 30) benzimidazolin-2tione, 31) dioxolanes (e.g. stiripentol), 32) azetidines (e.g. dezinamide), 33) triazoles (e.g. loreclezole), 34) acetamides (e.g. milacemide), 35) imidazoles (e.g. nafimidone), and other antiepileptic agents.

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(72) Inventor: LOMIA, Merab [GE/GE]; Corp. 3, Apt. 7, 166 Ambrolauri St., Tbilisi, 380060 (GE).

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(54) Title: USE OF ANTIEPILEPTICS FOR TREATING RESPIRATORY DISORDERS, IN PARTICULAR ASTHMATIC DISORDERS

(57) Abstract: This invention refers to medicine, in particular to pharmacology and pharmacotherapy. The technical result is to prevent specific expiratory bronchospasm in patients with bronchial asthma and other diseases and pathological conditions. The principally new indication provides use of antiepileptic agents for treatment of all types of bronchial asthma, status asthmaticus, asthmatic and allergic bronchitis, bronchial hyperreactivity and bronchospastic syndromes and treatment of diseases proceeding with these syndromes and also for treatment of allergic and vasomotor rhinitis and rhinoconjunctivitis.

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A. CLASSIFICATION OF SUBJECT MATTER
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 39091 A (PFIZER PRODUCTS INC.) 6 July 2000 (2000-07-06) claims 1-36	1,2
X,P	WO 99 58117 A (SANOFI-SYNTHELABO) 18 November 1999 (1999-11-18) claims 1-7 figure 1	1,2
X,P	WO 99 50255 A (NORTRAN PHARMACEUTICALS) 7 October 1999 (1999-10-07) claims 1-10,20,21,26,27,30,31	1,2
X,P	WO 99 43658 A (WARNER-LAMBERT COMPANY) 2 September 1999 (1999-09-02) claims 1,35,36	1,2

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[X] Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 176 928 A (BOEHRINGER INGELHEIM KG ET AL) 9 April 1986 (1986-04-09) claims 1-8 page 14	1,2
X	EP 0 176 929 A (BOEHRINGER INGELHEIM) 9 April 1986 (1986-04-09) claims 1-7 page 13	1,2
X	EP 0 338 892 A (SYNTHELABO) 25 October 1989 (1989-10-25) claims 1-12 page 13, line 26 - line 34	1,2
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X	FR 2 244 499 A (DELALANDE S.A.) 18 April 1975 (1975-04-18) claims 1-4	1,2
X	DATABASE WPI 'Online! DERWENT PUBLICATIONS LTD., LONDON, GB; AN: 1996-136303 '15!, XP002150396 & JP08027154 (Nippon Kayaku KK), 30 Jan. 1996 abstract	1,2
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...ormation on patent family members

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